

ROLE OF PROGNOSTIC NOMOGRAM AND SURVIVAL INDEX IN PROGNOSIS AND THE OUTCOME OF PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA - A SINGLE CENTER EXPERIENCETrajkova S.*¹, Cevreska L.¹, Stojanovic A.¹, Ivanovski M.¹, Petreska-Dukovska V.², Popova-Labachevska M.¹, Panovska-Stavridis I.¹¹University Clinic for Hematology, Skopje, Macedonia.²PH Remedika, Skopje, Macedonia.

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ABSTRACT

Introduction: Chronic lymphocytic leukemia (CLL) in its clinical course is a heterogeneous clonal lymph proliferative disease. Some patients live without the need for therapy for decades, while in others the clinical course is aggressive. Research focuses on the identification of biological factors that affect this heterogeneity. Clinical systems for division by stages Rai and Binet cannot identify whether the patient will have an indolent or progressive course of the disease. At Texas University, "MD Anderson Cancer Center" with statistical analysis, several independent features have been identified that predict the overall survival and a model composed of several independent parameters with which patients are divided into 3 risk groups has been created. A nomogram-prognostic model has been created that estimates the mean survival and predicts a probable total of five and ten years of survival using the six variables. **Aim of the study:** Evaluation of the applicability of the prognostic index and nomogram in terms of overall survival, prognosis in patients with CLL diagnosed and treated at the University's clinic for hematology in a period of ten years. **Material and Methods:** The study is set up retrospectively and includes 300 patients with CLL diagnosed and treated at the University Clinic of Hematology for a period of 10 years. The CLL diagnosis was made according to the recommendations of the International Working Group on Cholera (IWCLL). Clinical stratification was done as part of the prognostic index, and the nomogram was implemented according to the RAI system. With the help of the prognostic index, patients were stratified into three prognostic risk groups (low, intermediate, high risk), and according to the prognostic nomogram, the median survival and the probable five and ten years total survival were assessed. **Results:** The multivariate Cox Proportional model has confirmed ECOG and ALC that they affect the overall survival time. The estimated mean-median probability of 5-year survival according to the prognostic nomogram in patients with CLL is 77.5%, and the estimated Probability for 10-year survival according to the prognosis nomogram is 50.0%. **Conclusion:** The evaluation determined that the prognostic index and nomogram are reproducible in patients with CLL diagnosed and treated in R. Macedonia. Characteristics that predict total survival and survival without therapy have been identified.

KEYWORDS: Chronic lymphocytic leukemia (CLL), hematology, nomogram.**INTRODUCTION**

CLL is the most common type of leukemia found in the elderly in the developed world, especially in western and central Europe and in the United States.^[1] The incidence of the disease has an upward trend in R. Macedonia. Clinically, the disease is characterized by a variable course, with some patients never needing therapy and dying for reasons not related to the underlying disease, while other patients need treatment immediately after diagnosis. Clinical systems for division by stages Rai and Binet cannot identify whether the patient will have an indolent or progressive course of the disease.^[2] In addition to the factors used in the clinical division, there

are several patient characteristics and laboratory findings that are also correlated with overall survival, such as age, sex, type of bone marrow involvement, duplication of lymphocytes, presence of prolymphocyte in peripheral blood, bone marrow. There are other factors, such as biological, and which have a correlation with a poor prognosis, including the presence of chromosomal abnormalities such as 17 deletions, 11 deletions, elevated levels of B2-microglobulin, thymidine kinase, soluble CD23, unmutated variable genes of heavy immunoglobulin chain and increased expression of ZAP70 and CD38 in leukemic cells. Each of these prognostic factors alone has a limited influence on predicting overall survival.

Starting from these facts, at the University of Texas MD Anderson Cancer Center (MDACC), in order to identify the independent characteristics that predict the overall survival, untreated patients with CLL for 23 years were evaluated.^[3] Statistical analyzes identified several independent features that predict the overall survival, and a model composed of the following independent characteristics was created: age, B2-microglobulin, absolute number of lymphocytes, gender, Rai stage and number of lymph node groups affected by the disease, with which patients are divided into 3 risk groups. A nomogram-prognostic model has been created that estimates the median survival and predicts a total 5-year and 10-year survival using 6 variables. This prognostic model assists clinicians in clinical decisions for therapeutic choice, but also finds a place in clinical research. This prognostic index and nomogram has been evaluated by researchers at the Mayo Clinic in Rochester (MCR) with a confirmation of its significance.^[4] It does not contain established prognostic factors such as the mutational status of the variable genes of heavy immunoglobulin chain (IGHV), ZAP70, CD38 and chromosomal abnormalities (deletion11, deletion13, deletion17, trisomy12, etc.).

The motivation for this study is to evaluate the applicability of the prognostic index and nomogram in terms of overall survival, prognosis and adequate therapeutic approach in patients with CLL who have been diagnosed and treated at the University Hematology Clinic in Macedonia for a period of 10 years.

2. MATERIAL AND METHODS

2.1 Patients and specimens

The study was set up as retrospective and involved 300 patients with CLL diagnosed and treated at the University Clinic for Hematology for a period of 10 years (September 1, 2001 - September 30, 2011). The study was conducted at the University Clinic for Hematology in Skopje.

The diagnosis of patients with CLL was set according to the recommendations of the International Working Group on Cholera (IWCLL). In patients treated with chemotherapy, it was administered following a given written consent (Helsinki Declaration) and according to recommendations for treatment of the International Working Group on Cholera (IWCLL). All patients had pre-treatment evaluation which included:

Medical history of the disease; physical examination with a notched, two-dimensional diameter of the enlarged lymph nodes in all regions available for palpation (neck, axillar, supraclavicular, inguinal, femoral) The dimensions of the spleen and the liver are noted by physical examination - palpation. Where necessary, ECHO of the abdominal organs, CT chest and abdomen were used; performance status by ECOG; complete blood count with a certain number of leukocytes, platelets, hemoglobin value, differential

blood count with percentage and absolute number of lymphocytes; serum biochemical analyzes - biochemical markers with prognostic significance in which were investigated: serum LDH level, B2 microglobulin. Clinical stratification as part of the prognosis index with a nomogram was carried out according to the Rai system.

With the help of the prognostic index, patients with CLL diagnosed and treated at the University Hematology Clinic in the past 10 years were stratified into 3 prognostic risk groups (low, intermediate, high risk) and according to the prognostic nomogram they were assessed the mean survival and probably 5- and 10-year total survival. The actual survival of patients from 3rd groups was also evaluated. The validity of the nomogram and the index were shown statistically by comparison to the expected survival of risk groups obtained with the nomogram with actual survival calculated with the Kaplan-Meier statistical method.

2.2. Statistical analysis

All results were processed with the statistical program SPSS18 software program, and the results were displayed graphically and tabular. Here, methods of descriptive statistics, as well as nonparametric and parametric statistical analyzes, were used. In the series with attribute marks, a percentage and a structure are determined. The significance of the differences in the series with attribute marks was determined by applying the χ^2 test and the Mann-Whitney U test.

In series with numerical marks, the distribution of data with average, standard deviation, minimum and maximum value was tested. The relationship between two phenomena with numerical marks was determined by the Pearson coefficient of correlation (p). Differences between two independent numerical marks were determined by a t - test for independent samples. Differences between two independent samples with attributive marks were determined by Wilcoxon's test. Linear regression analysis and the Cox model were used to determine the relationship between various factors (clinical, biological) and the overall survival of patients with CLL. A log-test test (Kaplan Meier method) was used to determine the significance of the difference in survival among groups. Levels of probability for the realization of zero hypotheses, according to international standards for biomedical sciences, are 0.01 and 0.05.

3. RESULTS

The study was set up as a retrospective study involving 300 patients with CLL diagnosed and treated at the University Hematology Clinic for a period of 10 years. ((September 1, 2001 - September 30, 2011).

3.1.1 Epidemiological characteristics in diagnosis

The incidence shows the linear trend in the period 2001-2011 (graph1). The highest incidence rate in the analyzed population was registered in the year of 3.45 / 100.000

inhabitants, and the lowest in 2002, 0.7 / 100.000 inhabitants.

In terms of gender distribution, 64.7% of patients with CLL are male, and 35.3% are female, and the percentage difference is statistically significant for $p < 0.05$ ($p = 0.00000$) (graph2). The ratio male / female is 1.8: 1.

The mean age-Me is 66 years old. The most common age group with 58.3% is the age from 60 to 69 years, with the percentage difference in relation to other age groups statistically significant for $p < 0.05$ ($p = 0.0000$).

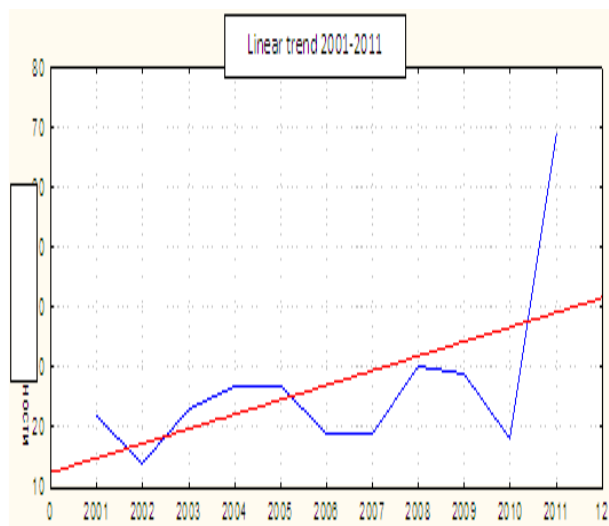


Chart no. 1: The linear trend of CLL for the period 2001-2011.

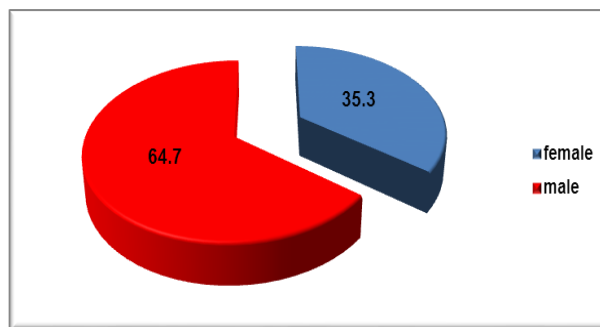
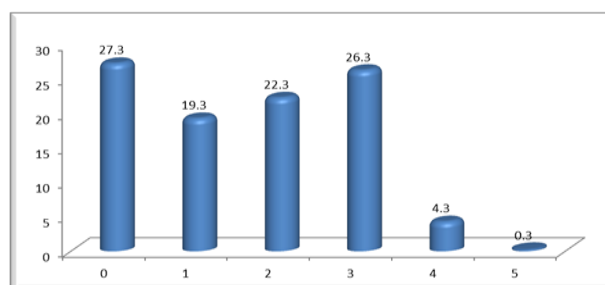


Chart no. 2: Graphical presentation of distribution of patients with CLL according to sex

3.1.2. Clinical features in diagnosis

The observed percentage difference recorded during the ECOG performance status survey is statistically significant for $p < 0.05$ (graph3).



Graph No. 3: Graphical presentation of the distribution of patients with CLL according to ECOG performance status.

Table 1: Review of the average values of laboratory trials in patients with CLL.

Parameters	No	%	min	max	St.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 2: Overview of absolute lymphocyte count values in patients with CLL.

ALC	No	%
<20	83	27.7
20 - 50	109	36.3
>50	108	36.0

According to the Absolute Lymphocyte Count (ALC) in patients with CLL, the percentage difference is statistically significant between values over 50, values 20 to 50 versus values below 20 for $p < 0.05$ ($p = 0.0295$).

Table 4: Distribution of patients with CLL according to the outcome.

Outcome	бpoj	%
Alive	128	42.6
Lost of follow up	50	16.7
Dead	122	40.7
All	300	100.0

In 40.7% of patients with CLL the outcome is death, in 42.6% the patients are alive, and 16.7% of the patients are lost from the records in the investigated period (Table 4).

3.1.3. Prognostic index and prognostic nomogram

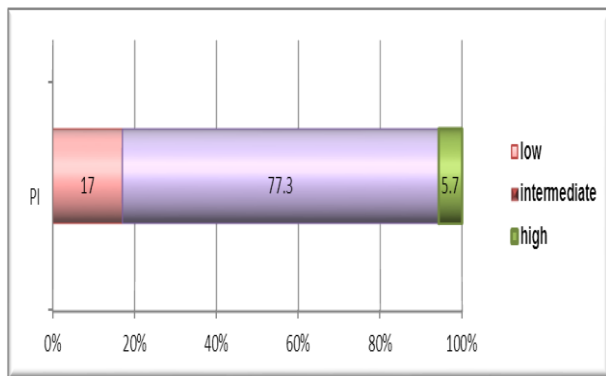


Chart no. 4: Graphical presentation of distribution of patients with CLL according to the prognostic index (PI).

The highest percentage of patients with CLL, 77.3% belong to the intermediate-risk group according to the prognostic index, 17.0% are low and 5.7% are at high

risk according to the prognostic index (graph 4), the percentage difference recorded between the middle risk versus the other two modalities (low and high) is statistically significant for $p < 0.05$ ($p = 0.0000$).

Table 5: Distribution of patients with CLL according to the prognostic nomogram.

Prognostic nomogram	No.	%
>80	197	65.7
<80	103	34.3
All	300	100.0

The highest percentage of patients with CLL, 65.7% belong to the prognostic nomogram group > 80 and 34.3% with prognostic nomogram <80 (tab.5), the percentage difference recorded between the two divisions of the prognostic nomogram is statistically significant for $p < 0.05 = 0.0000$.

Table 6: Distribution of Patients with CLL according to PI and immediately initiated therapy after diagnosis.

Immediately started therapy after setting the diagnosis Patients = 201	No.	%
PI low risk	20	9.9
PI intermediate risk	166	82.5
PI high risk	15	7.4

The highest percentage of patients with CLL, 83.5% with PI median, immediately started the diagnosis (Tab. 6), the percentage difference between the patient groups is statistically significant for $p < 0.05$ ($p = 0.0000$).

Table 7: Distribution of patients with CLL according to PI and estimated median survival.

Estimated mean survival Patients = 300	No.	years
PI low risk	51	15.9
PI intermediate risk	232	9.7
PI high risk	17	5.1

According to the prognostic nomogram in patients with low, intermediate risk and high risk stratified according to PI, the mean survival expressed in years (Tab. 7), with the longest mean survival of 15.9 years in low-risk patients, is estimated.

4.1.4. Statistical data processing

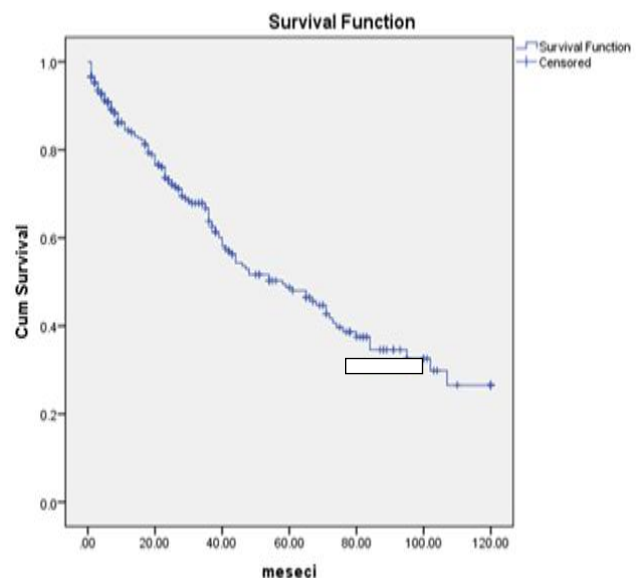


Chart no. 4: Overview of the overall survival time of patients with CLL.

Median survival in patients with CLL is 58 months (95% CI, 42.3-73.7). The calculated average survival yielded 63.1 months (95% CI, 42.3-73.7). Over 100 months survive 30.0% of patients with CLL.

Over 107 months survive 54.5% of patients with CLL, which according to PI are of low risk, 25.8% survive

over 107 months patients with CLL who according to PI are at medium risk, and patients with CLL who are at high risk of PI survive 32.0% (they survive 27.4 months and 40 months will not experience it) (Figure 5).

The difference between groups according to the prognostic index in patients with CLL in terms of overall survival is statistically significant for $p < 0.05$ (Chi-square = 31.07144 df = 2 $p = 0.00000$).

Median survival in patients with CLL with low risk of PI is 35 months, in patients with PIs with medium risk it is 23.5 months (95% CI, 30.8-57.2), which according to PI are at high risk is 7 months (95% CI, 6.7-15.3).

The calculated average survival in CLL patients with low risk according to PI is 95.9m (95% CI, 83.2-108.6), patients with CLL with medium risk are 58.9m (95% CI, 51.7-66.0), patients with CLL who are high risk according to PI are 15.4m (95% CI, 8.2-22.5) (Figure 5).

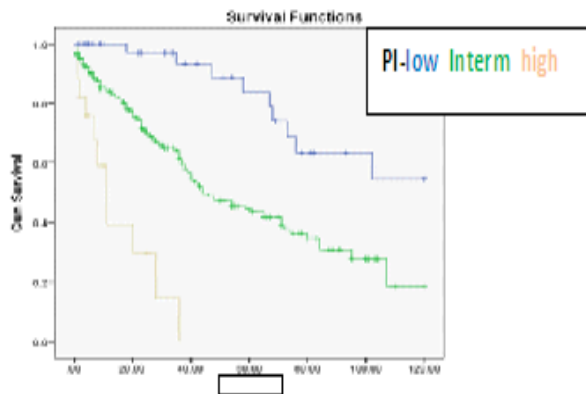


Chart no. 6. Overview of the overall survival time of patients with CLL according to the prognostic nomogram.

Table 8: Overview of the multivariate Cox Proportional model of the overall survival time of patients with CLL.

Variables in the Equation								
	B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp (B)	
							Lower	Upper
Gender			1.199	2	.549			
Gender (1)	.134	.224	.356	1	.551	1.143	.736	1.775
Gender (2)	1.060	1.061	.998	1	.318	2.885	.361	23.062
Hgb	-.247	.252	.961	1	.327	.781	.477	1.280
PLT	-.299	.226	1.748	1	.186	.741	.476	1.155
ALC	-.528	.242	4.759	1	.029	.590	.367	.948
ECOG			10.415	2	.005			
ECOG (1)	-.638	.256	6.201	1	.013	.529	.320	.873
ECOG (2)	-.756	.262	8.301	1	.004	.470	.281	.785
BINET			1.051	2	.591			
BINET(1)	-.429	.418	1.050	1	.306	.651	.287	1.479
BINET(2)	-.187	.296	.398	1	.528	.830	.464	1.482
Lymph. Nod	.089	.256	.122	1	.727	1.093	.662	1.806
Spleen	.358	.266	1.809	1	.179	1.430	.849	2.408
Liver	-.553	.286	3.724	1	.054	.575	.328	1.009
Coombs	-.118	.311	.144	1	.704	.889	.483	1.635
Albumin	-.111	.235	.223	1	.637	.895	.564	1.419

We evaluated the relationship between 19 factors of the overall survival time of patients with CLL. 11 (are predictors of the event) of 19 associate with the overall overall survival time of patients with CLL in univariate analysis.

However, the overall survival time did not associate with Rai, LDH, AP, IgM, IgG, IgA, Lym, WBC. (Tab.8).

The multivariate Cox Proportional model of the overall survival time of patients with CLL was confirmed by ECOG and ALC.

ECOG0 (fully active, capable of all activities without restrictions and ECOG 1 limited physical activity, but easy for easy physical activity eg home work, office work) Exp (B) (HR) -0.529 reduces the event by 47.1% every month (Tab. 8)

Exp (B) (HR) -0.470 reduces the event by 53% each month (Tab. 8) ECOG2 (outpatient but able to take care of itself but incapable of working activities, more than 50%.

The value of Exp (B) -0.590 (HR) for ALC reduces the event by 41% each month (tab 8).

The variables that are not statistically significant with the univariant model have been eliminated.

Table 9 Display at 5 years probability of survival by risk groups (prognostic index) in patients with CLL.

PI-risk group	5 years' time of survival	Standard error - SE
Low risk	.917	.036
Intermediate risk	.800	.011
High risk	.500	.091

Table 10: Display at 10 years probability of survival by risk groups (prognostic index) in patients with CLL.

PI-risk group	10 years time of survival	Standard error - SE
Low risk	.815	.011
Intermediate risk	.600	.015
High risk	.100	.065

The estimated probability of 5 years survival in patients with the prognostic index-lower risk is 0.917 (91.7%), and in 10 years survival 0.815 (81.5%). The estimated probability of 5 years survival in patients with the prognostic index-mean risk is 0.80 (80.0%), and in 10 years survival 0.60 (60.0%). The estimated probability of 5 years survival in patients with the prognostic index-high risk is 0.50 (50.0%), and in 10 years survival 0.10 (10.0%) (Table 9-10). The estimated median-mean probability of 5-year survival according to the prognostic nomogram in patients with CLL is 77.5%, and the estimated Probability for 10-year survival according to the prognostic nomogram is 50.0%.

4. DISCUSSION

4.1 Introduction to discussion

So far, we have mentioned several times that CLL has a heterogeneous clinical course. In terms of heterogeneity, some patients live only a few years after making the diagnosis, while others live decades without the need for treatment. In order to respond to heterogeneity and predict the prognosis, in the 1970s, the clinical systems for grading Rai and Binet were established. Today, the median survival of patients with CLL is estimated to be about 10 years apart from the past when it was 5-6 years in the years when they were introduced for the first time in everyday practice of the above-described systems of grading. The difference may be due to the fact that today the diagnosis is placed at an early stage of the disease, but further individual survival is very variable.

Today, in modern hematology, we experience the transition to personalized medicine. Conceptually, this means that patients will be treated with substances that target the tumor on the basis of individual molecular characteristics. But this personalized targeted therapy requires the identification of (bio) markers so that patients will be stratified according to the potential to respond to targeted therapy. Exactly CLL is an adequate model of disease due to clinical heterogeneity, high prevalence in western population, the presence of clinical and biological parameters. Heterogeneity of the disease refers to the natural history of the disease and the different outcomes of the same treatment in different patients. Genetic factors, age at time of diagnosis, the presence of co-morbidities are further potential factors

are contributing to the heterogeneity of the disease. Even in young patients with good performance, a status of a similar size of tumor mass has a difference in the occurrence of disease progression and response to therapy.

Considering the above, there was a need to find new biomarkers that would allow prognostic distribution of patients and adequate therapeutic choice. In addition to the established clinical systems, such as Rai and Binet systems and some laboratory parameters as time of duplication of lymphocytes, serum lactate dehydrogenase, many other markers have been identified and evaluated as prognostic factors in CLL. These markers range from those that are general markers that are determined in serum, blood, to protein markers that are detected by flow cytometry to specific genetic markers that are detected by specific laboratory methods such as determining the mutational status of the variable immunoglobulin molecule genes.

The patient's predictive factors are age, performance status, which in our retrospective study with the multivariate Cox Proportional model for overall survival of patients with CLL confirmed the ECOG performance status as a factor that affects overall survival.

There is no doubt that there is a need to discuss the usefulness of prognostic markers in the clinical diagnosis, but also the need to introduce new predictive and prognostic markers that would be therapy guides, so that we can combine these markers as a "prognostic index for CLL".

4.2 Prognostic Index and Prognostic Nomogram

Wierda WG.^[3] in the study published in 2007, presented a prognostic index and a nomogram designed to predict the clinical outcome and overall survival. Clinical systems for grading Rai and Binet identify risk groups based on clinical and laboratory characteristics. In essence, the stage correlates with survival, but each stage is characterized by heterogeneity, which limits the prediction of full survival. There are other prognostic and predictor factors that are not part of the clinical systems for grading Rai and Binet, and correlate with poor outcome, such as 17r deletion, 11q deletion, elevated B2b level of microglobulin, unmutated immunoglobulin

genes, expression of CD38. But everyone has limited power to predict the clinical outcome and overall survival. That was the starting point of the Wierda WG.^[3] to create a nomogram as a graphic representation of a statistical model with scales for calculating the commutative impact of the measured variables on the probability of the outcome. The nomogram estimates the likelihood of outcome, and even death, it has the power to combine the variables to predict the outcome.

The nomogram was created to predict survival using six independent covariance's identified in a multivariable model. The end result identifies the likelihood of a 5- and 10-year survival and estimates the median survival. Each variable has its place with the greatest influence in the end result, the first two years, B2M globulin and absolute lymphocyte count (ALC), followed by sex, Rai III and IV stage and the presence of 3 groups of the palpable lymph nodes. The median result of all patients was 82.9 with a range of 31.5-187.2. In the study of Shanafelt *et al.*^[4] the median score of all patients was 83.9. In our study the average value of the prognostic nomogram is 87.5, the score ranges from 38 to 136, and the median on the score of the nomogram is 87.0 data that are in accordance with the published studies.^[3,4]

The prognostic index was created using 6 prognostic factors each of which was valued at one point. The patients are divided into three risk groups as low, intermediate and high. In our study 77.3% belong to the group with intermediate risk according to the prognostic index, and the percentage difference recorded between the intermediate risk versus the other two modalities (low and high) is statistically significant for $p < 0.05$ ($p = 0.0000$). These data differ from those published in the Wierda WG study.^[3] where the largest percentage of patients belonged to the low-risk group, while in our study the highest percentage belonged to the intermediate-risk group.

The estimated mean survival for low risk was not achieved in the Wierda WG study and collaborative.^[3] the mean survival for intermediate risk was 10.3 years and 5.4 years for high risk. In our study, the estimated survival for the low-risk group is 15.9 years, for the intermediate risk group is 9.7 years, and 5.1 years for the high-risk group. Those data are closer to the presented by the Wierda WG study and collaborators.^[3]

Percentage of probability of 5-year survival in the study of Wierda WG.^[3] in the low-risk group is 0.97 (97%) and the probability of 10-year survival is 0.80 (80%). The mean risk group has a 0.80 (80%) probability of 5-year survival, and the likelihood of 10-year survival was 0.52 (52%), and the probability of a 5-year survival rate of 0.55 (55%) for the high-risk group, while the likelihood of 10-year survival was 0.26 (26%).

Similar results were noted in our study, with a low risk group of 0.917 (91.7%), and in 10 years survival 0.815

(81.5%). The estimated probability of 5 years survival in the prognostic index -mediate risk is 0.80 (80.0%), and in 10 years survival 0.60 (60.0%). The estimated probability of 5 years survival in the prognostic index-high risk is 0.50 (50.0%), and in 10 years survival 0.10 (10.0%).

This model is valid for untreated patients, regardless of the time the diagnosis is made, and can be used serially for the same patient at the time when the next treatment is planned.

In our study, the multivariate Cox Proportional model during overall survival showed the ECOG status of 0.1.2 and ALC as factors that influence overall survival.

Other authors also use the prognostic index to predict the survival of patients with CLL. Molica S. and coll. used this prediction index for the time to first treatment but only in patients with the early stage of CLL, Binet A.^[6] A classification tree was constructed that identified three subgroups of patients with low, intermedium and high risk. The probability of 5-year-time without therapy was 100% for the low-risk group, 81.2% for the mid-risk group, and 61.3% for the high-risk group.

Patients in the early stage are very heterogeneous and therefore the use of the predictive index is of great importance. Pepper and coll. also used this group of patients in the early stage of the disease to target 70% of patients with CLL in order to define which patients would need therapy.^[7] They present a large study with patients with BineA, with the ultimate goal of defining factors that influence total survival and time to first therapy. Multivariate analysis has shown that only the time of duplication of lymphocytes, the mutational status of immunoglobulin genes, CD38, and age when placing diagnosis are independent variables that affect total survival and time to first therapy. With the conclusion from the study that the mutational status of immunoglobulin genes, CD38 have an independent prognostic value to patients with early stage of CLL and that they should be part of the prognostic models in everyday work.

The Italian group of authors proposed a new prognostic index for patients with CLL, with prior testing of the prognostic power of biological, clinical and demographic variables in the multivariate model.^[8] The ultimate goal of the study was to determine prognostic factors (mutational status, high risk chromosome aberrations such as 17r deletion, 11q deletion, expression of CD38, ZAP-70, age, gender, Binet stage, B2M, ALC, number of regions with elevated nodes) which could affect overall survival. In the multivariate model, the mutational status, high-risk chromosomal aberration as a 17d deletion was a biological variable with an independent prognostic value. The time until first therapy in patients with BineA and younger than 70 years depended on the mutational status as the most important predictor. This group of

researchers created a clinical and biological prognostic index comprised of 6 variables composed of Binet stage, age, gender, B2M, presence / absence of unmuted immunoglobulin genes, presence / absence of 17p deletion. Patients were classified into three risk groups as a group with a low, intermedium and high risk, and projected a 5-year full survival rate of 98%, 90% and 58% for low-, intermedium - and high-risk groups, and offered a nomogram for an individual survival assessment in each patient. The proposed prognostic index and nomogram passed only through internal validation. For wider acceptance and implementation, external validation is required.

A step ahead went to the research group of Hallek M. and collaborators which faces the fact that as an addition to the clinical systems, Rai and Binet have a number of biomarkers that predict the overall survival, but they all give us limited information about what their independent prognostic value is and how to incorporate them into everyday work.^[9] An analysis of 23 prognostic markers was performed on the basis of a large number of patients who participated in phase 3 of the clinical studies of the German CLL group in order to create a comprehensive prognostic index. The multivariate analysis of the identifier fictional 8 independent predictors of total survival such as sex, age, ECOG status, deletion 17p and deletion 11q, mutational status of immunoglobulin genes, serum B2M levels, serum thymidine kinase. The 17p deletion is the highest scoring factor. Using a gradation system, a prognostic index with 4 risk groups was created with a 5-year full survival ranging from 18.7% to 95.2%. This prognostic index was subjected to an external validation confirmed by a group of patients from the Mayo Clinic. With the help of statistical processing and external validation, a comprehensive prognostic index with high power discrimination and a forecast for each patient on an individual level was created.

This comprehensive prognostic index was evaluated by the original index created by Wierda WG.^[3] and it could provide great applicability, increase the accuracy of the prognosis apart from the classical grading systems, but it will also provide an individualized therapeutic approach. And it is already implemented in clinical research aimed at development of treatment algorithms.

In the future in our daily work, besides the prognostic index and nomogram for determining the overall survival, whose validity we showed and the possibility for reproduction, we could also use the prognostic nomogram also proposed by Wierda WG.^[5] to determine, calculate the 2- and 4-year probability of treatment, and estimate the median time to treatment.

5. CONCLUSIONS

1. The study established the epidemiological data in patients with CLL diagnosed, treated at the University Hematology Clinic, with a tendency to increase the

incidence of CLL in 2011, and the highest incidence of male sex.

2. The evaluation determined that the prognostic index and nomogram are reproducible in patients with CLL in R. Macedonia and they can assess the median survival and determine the probability of total 5-year survival, the largest percentage of patients belonging to the group with an intermediate risk according to the prognostic index and prognostic nomogram score > 80.

3. Predictive, prognostic factors that predict the overall survival are ECOG 0, 1,2, ACB, but the overall survival is also influenced by gender, age groups, prognostic index and prognostic nomogram, Rai and Binet stage.

6. LITERATURE

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